Predictors of Improvement in P300 Latency in Solvent-Exposed Adults

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Summary: Persons with a history of exposure to organic solvents have been shown to have cognitive and personality changes, as well as abnormalities on measures of neurophysiology (e.g., delays in P300 latency). Studies assessing long-term sequelae in exposed persons have been limited, especially those using neurophysiologic measures. This study assessed cognitive event-related potentials (ERPs) in 16 persons with a history of organic solvent exposure at two testings, separated, on average, by 1.5 years. The sample was divided into persons who showed improvement on P300 latency (e.g., reduction in latency of 1.5 SD of control group) and those who did not. Sixty-three percent showed no improvement, whereas 37% showed significant improvement. Recency of exposure and the interaction of exposure duration and history of peak exposure significantly predicted group membership. That is, persons with shorter duration of exposure coupled with no peak exposures and longer time from exposure to test were more likely to fall in the improved group. Substituting age for duration of exposure in the interaction term improved classification of the two groups. The results support previous findings that most exposed persons do not show significant improvements over time. The results further suggest that there is a need to assess factors, such as aging, which may make one more vulnerable to the neurotoxic effects of solvents. Key Words: Event-related potential—P300—Solvent exposure. NNBN 11:146–150, 1998.

It is estimated that more than 9 million persons in the United States are exposed to organic solvents in the workplace each year (1). Solvents are lipophilic and thereby target central nervous system (CNS) tissue. Although adverse cognitive and psychiatric changes in persons with chronic exposure have been reported in the literature for more than a century (for a review see [2]), the existence/extent of CNS damage is still debated, particularly regarding long-term sequelae (3). A few solvents, particularly n-hexane, have been shown to produce neurologic symptoms (e.g., neuropathy) that may worsen over time (4), but most health professionals think that cognitive and behavioral symptoms should resolve after removal from the exposure (5). However, the few studies that have studied long-term outcome on cognitive performance and psychiatric and neurologic symptoms have reported only approximately a 25% to 50% improvement in exposed persons after removal from the exposure (6–10).

Objective evaluation of neurophysiologic function (e.g., functional neuroimaging, event-related potentials) in solvent-exposed persons has been limited, and studies have typically assessed subjects at only one point in time. Several reports have demonstrated decreased blood flow to various cortical and subcortical areas using positron emission tomography (PET) and single photon emission computed tomography (SPECT) in persons with acute high levels of exposure or long-term chronic exposure (11–14). Measurement of the event-related potential (ERP) has also documented abnormalities in exposed persons, and a significant delay in the latency of the P300 component of the
ERP has been observed in solvent-exposed persons compared to nonexposed controls (15,16). Moreover, in 50% of solvent-exposed patients, the mean P300 latency (387 msec) exceeded the control group mean (346 msec) by more than two standard deviations (SD) (15). Changes in the EEG over time in patients with “chronic solvent poisoning” have been examined by Seppäläinen and Antti-Poika, who found a 59% improvement in slow wave abnormalities but an increase in “paroxysmal abnormalities” (17).

The question of whether objective measures of neurophysiologic function remain stable or improve in exposed persons after removal from the exposure has not been sufficiently addressed. Moreover, there has been little consistent work in determining which exposure-related variables are important in determining outcome. Duration of exposure (usually expressed as number of years working with solvents) and recency of exposure are the two variables most often assessed. However, number of years working does not take into account episodes of peak exposures, which have been shown to predict poor cognitive outcome (i.e., no change or decreased test scores) in solvent-exposed persons over time (9). Seeber (18) also noted that persons with episodes of intermittent peak exposure to solvents had higher rates of abnormality on psychological measures than persons who were exposed to chronic low doses. A recent study that assessed journeyman painters with ongoing solvent exposure found a significant association between performance on learning and memory tests and the interaction of lifetime exposure and current, acute exposure (19).

For this study, we compared cognitive ERPs in a group of solvent-exposed adults at two testing sessions, separated on average by 1.5 years. Our hypothesis was that longer duration of exposure, coupled with a history of peak exposure, would be associated with adverse neurophysiologic outcome (i.e., increases or lack of improvement in P300 latency) over time. In addition, we assessed the contribution of recency of exposure—the amount of time between the exposure and testing—to predict changes. The hypothesis being that no improvement in P300 latency would be associated with shorter intervals between exposure and testing.

METHOD

Subjects

The study sample consisted of 16 adults from the ages of 27 to 54 years (mean = 43.06, SD = 8.44) with a history of exposure to organic solvents and neuropsychiatric complaints. All subjects had initially been seen by an occupational health physician, and neuropsychological testing was consistent with mild solvent encephalopathy (3). Data from four of these subjects were included in an earlier report (15). No person had a history of prior neurologic injury or psychiatric disorder, alcohol consumption exceeding one to two drinks daily, or hearing impairment that precluded accurate perception of stimuli based on auditory screening. A detailed occupational exposure history was taken for each subject to determine type and duration of exposure, exposure-to-test interval, and whether there had been any past episodes of peak exposure that required treatment from a health professional.

At the initial evaluation, the average exposure-to-test interval was 15 months (range, 2 weeks to 10 years). The second testing was done, on average, 20 months after the initial testing (range, 9 months to 3 years). None of the subjects had an intervening exposure between the two testing sessions: all subjects had either left the workplace or transferred to a work location where they had no exposure. One third of the subjects reported at least one peak exposure—an episode in which they had been exposed to an excessive amount of solvent that resulted in a visit to a doctor or hospitalization. The average exposure duration for the subjects was 6.2 years (range, 1 day to 30 years). All subjects had been exposed to mixtures of organic solvents (e.g., toluene, benzene, xylene) and the primary route of exposure was inhalation, although some also had direct dermal contact with the solvents. The study was approved by the University of Pittsburgh School of Medicine and VA Pittsburgh Healthcare System review boards. After explanation of the testing, informed consent was obtained from all participants.

Cognitive Event-Related Potentials

An auditory “odd-ball” paradigm was completed in a counting and reaction time (RT) paradigm using a Grass Instrument Model 12 Neurodata (West Warwick, RI) system. Infrequent (25%) high tones (1500 Hz) or frequent (75%) low tones (800 Hz) were presented at 3-sec intervals for 40-ms duration (65 dB). Subjects were informed that high-pitched tones were less frequent and would not occur in succession; all other stimulus presentation was determined by pseudorandomization. In the counting task, the subject counted the number of infrequent high tones during each of two successive blocks (80 trials/block). In the RT task, the subject pressed different buttons for the high or low tone on each of two successive blocks (counterbalanced for responding hand). The counting task was always done before the RT task. Stimulus presentation, digitization of electrophysiologic data, and initial data reduction were performed with a Digital Equipment Corp. (Maynard, MA) PDP-11/73 (MINC) computer system.

The electroencephalogram (EEG) (bandpass 0.01–30 Hz) was recorded from scalp electrodes at midline, frontal, central, parietal, and occipital and lateral parietal locations (Fz, Cz, Pz, Oz, P3, P4) referred to linked ears. Data were digitized at 8-ms intervals for 1200 ms, beginning 200 ms
before stimulus onset. Ocular artifacts and blinks were monitored with vertical electrooculogram (EOG). Averaged ERPs were calculated from artifact-free single trials (<75 µV range) with all incorrect trials (errors in responding on the RT task) excluded from the analysis. Across subjects and tasks, each average response was comprised of a mean of 30 individual trials.

Test-retest reliability of P300 in our laboratory is good to excellent. Test-retest reliability for patients and other subjects demonstrate high correlations for the Counting (0.71 to 0.97, p < 0.01) and Choice RT (0.64 to 0.85 p < 0.01) tasks. Data for this report are based on P300 latency (Pz) from the infrequent high-tone condition for the counting and RT tasks. A computer algorithm identified component peaks and these were verified by two raters that were blind to subjects' status.

**Procedure and Data Analysis**

The focus of this study was to evaluate outcome defined by a measure of neurophysiologic activity, P300 latency, that has previously been shown to be altered in solvent-exposed adults. Moreover, the objective was to determine whether there were changes over time and, if so, the extent to which exposure variables related to these changes. To that end, subjects were divided into two groups: those whose P300 latency improved at the second testing and those who showed no improvement. Improvement was defined as a decrease in latency on the counting or choice RT task by more than 1.5 SD compared to the group as a whole or a latency that at the second testing was within 1 SD of the "normal" range. That is, a person was coded as improved if, on the second testing, P300 latency for counting decreased by at least 44.8 msec (49.5 msec for the choice RT), or decreased to below 376 msec (based on previous normals for normal controls from this same laboratory) (15).

Discriminant function analysis was used with group (improved vs. nonimproved P300 latency) as the criterion variable. Recency of exposure and the interaction term—duration of exposure × peak exposure (treated as a dummy variable)—were entered as predictor variables. The interaction term was created because of the hypothesis that longer duration, coupled with a history of peak exposure, adversely affects outcome.

**RESULTS**

There were five subjects who exhibited improvement in P300 latency between sessions on at least one task and 10 subjects who did not. Table 1 presents demographic data, exposure data, and P300 latency measures for the two outcome groups. The difference in latency between the groups can be seen at the bottom of the table: the improved group showed a change in latency from 416 msec at the first testing to 366 msec at the second testing on the counting task. In contrast, the group with no improvement had a P300 latency at the first testing of 399 msec and showed similarly prolonged times, 405 msec, at the second testing. Comparable results were noted for the choice RT task: 397 msec to 352 msec for the improved group and 396 msec to 393 msec for those subjects who did not improve. The difference between the two testings was significant for the improved group (Wilcoxon Signed Ranks Test, p = 0.05).

A two-group discriminant analysis involving the two exposure-related independent variables (recency and duration × peak exposure) yielded a significant function (R = 0.654, F = 4.864, p = 0.026) and correctly classified 81.3% of the cases. That is, those persons who had longer exposure duration combined with a history of peak exposure, as well as less time between their last exposure and the testing, were more likely to be in the poor outcome group.

Inspection of the table shows that the improved group was also younger and better educated. Age and duration of exposure, not surprisingly, are often correlated because the older one is the more likely one is to have worked longer and therefore had more exposure. In this sample, there was a moderate correlation between age and duration of exposure (r = 0.58, p = 0.05). Because of the small sample size and because age and exposure were correlated, we did not add age into the original model. However, when we re-ran the analysis and substituted age for duration of exposure in the interaction term, the classification of the two groups improved to 93% (R = 0.89, F = 26, p < 0.001). However, education was not correlated with latency in the total group or the two outcome groups at the first or second assessment. Therefore, we did not add education to the model.

Note also that we have previously reported that nonexposed normal controls from our laboratory have P300 laten-

<p>| TABLE 1. Demographic characteristics, exposure data, and P300 latency for two groups |
|-------------------------------|---------------|---------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Improvement</th>
<th>No Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>No. of females</td>
<td>15.5 (4.0)</td>
<td>12.2 (1.7)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>15.2 (6.8)</td>
<td>22.5 (12.1)</td>
</tr>
<tr>
<td>Test-retest interval (months)</td>
<td>35.9 (71.5)</td>
<td>99 (116)</td>
</tr>
<tr>
<td>Duration of exposure (months)</td>
<td>20 (8.7)</td>
<td>12.7 (14.4)</td>
</tr>
<tr>
<td>No. of peak exposures</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Mean SD</td>
<td>38.4 (6.0)</td>
<td>45.8 (8.6)</td>
</tr>
<tr>
<td>Mean SD</td>
<td>39.8 (6.2)</td>
<td>47.2 (8.6)</td>
</tr>
<tr>
<td>Counting latency time 1</td>
<td>416 (26.7)</td>
<td>399 (31.2)</td>
</tr>
<tr>
<td>Counting latency time 2</td>
<td>366 (38.3)</td>
<td>405 (41.6)</td>
</tr>
<tr>
<td>RT latency time 1</td>
<td>397 (23.0)</td>
<td>396 (38.8)</td>
</tr>
<tr>
<td>RT latency time 2</td>
<td>352 (29.5)</td>
<td>393 (26.8)</td>
</tr>
</tbody>
</table>
P300 LATENCY IN SOLVENT-EXPOSED ADULTS


cies in the range of 343 to 346 msec (15). Because of the discrepancy in age between the improved and nonimproved groups in this study—a little more than 7 years—we calculated P300 latencies for control subjects in the same age ranges (24 to 39 and 39 to 53). The latencies for the counting and choice RT tasks for normal controls in these age groups were similar to what we have reported before and did not differ by more than 6 msec across the tasks (range, 346 to 352 msec).

DISCUSSION

The primary goal of this study was to determine whether solvent-exposed persons who are characterized by delays in P300 latency at initial testing demonstrate changes over time. It was hypothesized that certain exposure-related variables, namely recency, as well as duration and history of peak exposure, were predictive of outcome. Findings showed that most subjects did not show improvement in P300 latency. That is, 63% of the group did not show decreases in P300 latency between the two testing sessions. This percentage is slightly higher than previous longitudinal follow-up studies of solvent-exposed subjects in whom improvement on cognitive, neurologic, and physiologic measures averaged approximately 50% (6.8–10). The 37% of subjects in this sample who showed improvement differed in demographic and exposure-related variables from those who showed no improvement. The lack of a history of peak exposure, shorter duration of exposure, and longer interval between exposure and testing were predictive of improved P300 latency. However, as noted, the improved group was also younger and better educated than those persons who showed no improvement. Whereas education was not correlated with P3 latency, age was significantly correlated with exposure duration. When age was substituted for duration of exposure in the model, the percentage of subjects correctly classified increased from 81% to 93%

It is difficult to determine with this sample size what factor is most critical in driving the results, the age of the person or the duration of the exposure. Age has typically been included as a covariate in studies assessing cognitive effects of solvents. How age may interact with exposure variables, such as a peak exposure, has not been addressed systematically. Researchers have suggested that an aging brain may be more susceptible to the effects of solvent exposure, possibly because of depleted functional reserves, or the toxin may produce an accelerated loss in specific neural systems that results in premature aging (20,21). The current data support the consideration that a vulnerability to the effects of solvents may be related to individual factors, such as age. At this point we cannot separate the effects of duration of exposure and age but either one or both may play a significant role in contributing to neurophysiologic outcome over time.

Prior research looking at changes in cognitive function also found evidence of a history of peak exposure to be significantly related to poor neuropsychological outcome (9,18). Other researchers have also speculated that intermittent peak exposure, coupled with low-level chronic exposure, may be particularly injurious to brain function. Bell and colleagues have argued, based on studies of animals and humans, that an initial peak exposure may alter or trigger certain neural systems, particularly those connected to the amygdala and hippocampus, such that continued, repeated low-level exposure leads to “progressively increased levels of responsivity over time in those structures” (22). This increase in “sensitization” could then account for the behavioral and cognitive changes, as well as produce alterations in neurophysiologic function, including delays in P300 latency. That there was no improvement in neurophysiologic outcome in persons with longer duration of exposure and a history of peak exposure may result from neural sensitization in brain regions associated with the generation of P300. Multiple cortical and subcortical sites have been implicated in the origin of P300, including the hippocampus and amygdala (23–26).

Our prior work, which found peak exposure to be predictive of poor cognitive outcome, found increased psychiatric stress to be higher in the group of exposed persons whose neuropsychologic test scores did not improve (9). For the current sample, data were available from the Symptom Checklist 90-R (27) for five subjects in the improved group and seven subjects in the nonimproved group. We subsequently reviewed scores on this measure for the two outcome groups. There was no evidence that persons whose P300 did not improve had greater severity of psychiatric symptoms. SCL-90-R scores in the poor outcome group were slightly lower at the initial and follow-up testing (raw scores = 144 and 135, respectively) compared to persons whose P300 latency improved (raw scores = 166 and 145, respectively). Prior research has also shown that P300 latency is not associated with mood or affective state (28,29). Therefore, in this sample, it is unlikely that alterations in neurophysiologic function are attributable to psychological distress.

We evaluated amplitude values for the two groups and found no pattern of amplitude change based on group membership. That is, for those five subjects who improved, amplitude measures across the two tests were virtually the same at 9 μV at each testing. The poor outcome group had a decrease in amplitude across the testing on the counting task (9 μV to 7 μV) but an increase on the choice RT task (9 μV to 10 μV).

The data gathered suggest that for solvent-exposed persons with abnormal prolongation of P300 latency, this prolongation continues for most individuals even after removal from the exposure. Because our sample was relatively small, we were limited in testing variables to predict

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change. However, our hypotheses that longer duration combined with a history of peak exposure and a more recent exposure would relate to poor outcome were confirmed. Future studies will need to address additional variables, particularly age or other factors that may compromise brain function (e.g., hypertension, diabetes) and thus make one more vulnerable to the neurotoxic effects of solvents.

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